REMARKS

This paper is responsive to the Office Action dated April 7, 2004, which is the first action on the merits of the application.

Claims 1-16 were previously pending in the application and under examination. Upon entry of this Amendment, claims 17-20 are added. The added claims depend from claims previously considered, and fall within the group under examination. Accordingly, claims 1-20 are now pending in the application and under examination.

Further consideration and allowance of the application is respectfully requested.

Claim amendments:

Entry of the claim amendments does not introduce new matter into the disclosure.

Reference for the derivation strategy and reagents of this invention as a "system" (claim 1) is stated on page 4, lines 3-4, and page 6, lines 19-20. The use of hES cells as exemplary pPS cells (claim 2) was presented in claim 1 as filed. New claim 17 presents a feature previously appearing in claim 1. Claim 18 is supported by claim 9 and throughout the disclosure. New claim 19 echoes claim 4. New claim 20 echoes claims 14 and 15.

No new limitation is added to claim 1, except to indicate that the differentiated cell population is part of a system for obtaining hepatocyte lineage cells. Otherwise, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Double Patenting and Terminal Disclaimer

Certain claims stand provisionally rejected for obviousness-type double patenting over certain claims of copending application USSN 10/001,267.

Applicant acknowledges this rejection. Upon indication of the subject matter otherwise patentable in this and the other application, applicant hereby undertakes to file a terminal disclaimer in one or the other application, or take other appropriate action to obviate double patenting.

Other claims stand rejected over claims for obviousness-type double patenting over issued U.S. Patent No. 6,506,574.

Enclosed herewith is a Terminal Disclaimer with respect to the '574 patent.

Rejection under 35 USC § 112 ¶ 2:

Claims 1-16 stand rejected under § 112 ¶ 2 as being indefinite.

Use of the symbol "~" in claims 1 and 2 is replaced by the term "about", which is its ordinary meaning.

Use of the term "about" in claims 1, 2, 3, and 4 meets the requirements of § 112 ¶ 2. MPEP § 2173.05(b)(A) provides a detailed analysis of the relevant case law. Briefly, the term is generally acceptable for defining a range for a variable, or the lower limit for a variable. *Ex parte Eastwood,* 163 USPQ 316 (Bd. App. 1968); *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 220 USPQ 303 (Fed. Cir. 1983). The term may be indefinite under the requirements of § 112 ¶ 2, only if two conditions are present: there is close prior art, AND there is nothing in the specification, file wrapper, or prior art to provide an indication as to what range is covered. *Amgen, Inc. v. Chugai Pharmaceutical Co.,* 18 USPQ2d 1016 (Fed. Cir. 1991).

In the present instance, the Office has not identified any close prior art in which close to 60% of the cells in a differentiated cell population obtained from pPS cells have the characteristics of hepatocyte lineage cells as listed in the claims. The analysis therefore fails to provide one of the requirements needed to challenge the use of the term "about" in the pending claims under 112 ¶ 2.

The skilled reader will readily understand that the phrase "at least about 60% [of the cell population]" means that a substantial proportion but not necessarily all of the cells in the population will have the characteristics referred to. The phrase is used in the claims partly as a convenience to the reader who wishes to put this invention into practice. It saves them from expending the resources to count and analyze a large cell population, in order to be statistically certain whether at least exactly 60.000% of the cells meet the criteria of the claimed invention.

Claims 9 and 13 have been amended in a manner that is believed to obviate the rejection. Applicant thanks the Examiner for providing the opportunity to make this correction.

Withdrawal of these rejections is respectfully requested.

Rejection under 35 USC § 102:

Claims 1-8 and 14-16 stand rejected under § 102(b) as being anticipated by a published article by Kaneko et al. (Cancer Res. 50:3101, 1990). The Office Action indicates that the Chang liver cells used by Kaneko et al. are indistinguishable from the hepatocyte lineage cells referred to in the claims.

Applicant respectfully disagrees. An important benefit of the invention claimed here is that it provides to the public for the first time a virtually unlimited source of primate hepatocytes having the same genome and growth characteristics.

Previous to the making of this invention, there were only two principle sources of primate hepatocyte like cells.

The first was to separate cells from liver tissue obtained from a whole animal. However, cells isolated from human liver have only a very limited replicative capacity, and will not survive in tissue culture for very long. Furthermore, the population as a whole contains a substantial proportion (perhaps 30%) that are types of liver cells different from hepatocytes: specifically, sinusoidal endothelial cells, bile duct epithelial cells, and Kupffer cells (macrophage lineage cells). None of these cells has substantial cytochrome p450 activity, and none plays the same role in detoxification and nutrient processing as do hepatocytes. Because of the limited ability for the hepatocytes to replicate after isolation, the undersigned knows of no procedure by which a population can be produced that contains primate hepatocytes, but none of these other liver cell types.

The other source of hepatocyte like cells available before the making of this invention is the use of cell lines having hepatocyte characteristics derived from cancer cells. Malignant transformation of the line gives the cells a high replicative capacity. However, because the cells are cancerous, they typically have other genetic changes which affect growth and other aspects of cell behavior. For this reason, the pharmaceutical industry is reluctant to use cancer cell lines for purposes of drug testing, and ultimately relies on isolated hepatocytes (in spite of their limitations).

The present invention provides an important new source of hepatocyte lineage cells for potential use in drug screening and therapy. Human ES cells have a virtually unlimited reproductive capacity: Amit et al., "Clonally derived human embryonic stem cell lines maintain pluripotency and proliferative potential for prolonged periods of culture", Dev. Biol. 227:271-278, 2000; Rosler et al., "Long-term culture of human embryonic stem cells in feeder-free conditions", Dev Dyn. 229:259-274, 2004. This provides a virtually unlimited source of hepatocyte lineage cells according to this invention, regardless of the replicative capacity of the hepatocytes themselves. The hES cells can be grown in the undifferentiated state to whatever volume is required, and then differentiated into

hepatocytes as described in the specification before use. More hepatocytes having the same characteristics can be generated from the same hES cell line as needed.

Claim 1 has been amended to distinguish the hepatocytes of this invention from prior art cells by indicating explicitly that they are part of a *system* that also comprises the pPS cells from which they were derived. Since the cells in the Kaneko reference were not derived from isolated pPS cells, there is no matched set of pPS cells (i.e., pPS cells having the same genome) that meet the definitional requirements indicated in the specification (page 9, lines 19-24). As already explained, the matched pPS cells are important, because they allow the user to obtain more of the differentiated cells, as needed.

Claim 2 distinguishes the hepatocytes of this invention from prior art cells by requiring: a) that the differentiated cells are karyotypically normal and non-malignant; and b) that the cell population comprises less than 0.1% endothelial cells or Kupffer cells.

Although the Kaneko reference may have thought that Chang liver cells were derived from normal liver cells in 1990, it has been proved they were actually derived from a malignant cell source.

Enclosed with this paper is information obtained from the ATCC website, showing that Chang liver cells (deposited by R.S. Chang) are derived from HeLa cells. The commentary states the following:

> This line was originally thought to be derived from normal liver tissue, but was subsequently found, based on isoenzyme analysis, HeLa marker chromosomes, and DNA fingerprinting, to have been established by HeLa cell contamination.

The ATCC information on HeLa cells indicates that HeLa marker chromosomes have a combination of rearrangements in chromosomes 1, 3, 5, 11, and 19. Since Chang liver cells have HeLa markers, they are *not karyotypically normal.* The definition of HeLa cells enclosed with this paper (obtained from the Webster's Online Dictionary website) confirms that HeLa cells were derived from the *cervical carcinoma* of Henrietta Lacks. Accordingly, *Chang liver cells are malignant cells.* Accordingly, the cells referred to in the Kaneko reference fail to meet two of the limitations required by claim 2.

For the same reasons, any hepatocyte line derived from malignant or malignantly transformed cells cannot anticipate the invention embodied in claim 2.

As already explained, claim 2 is also not anticipated by hepatocyte cell populations isolated from normal liver tissue, because such cell populations will inevitably be contaminated by endothelial cells and/or Kupffer cells.

Accordingly, claim 1, claim 2, and all claims depending therefrom are distinguished over previously known cell populations. The claimed invention meets the requirements of 35 USC § 102.

Information Disclosure Statement

Applicant is grateful to the Examiner for considering the information provided in the preceding Information Disclosure Statement.

A further IDS under 37 CFR § 1.97(c)(2) along with the requisite fee accompanies or will shortly follow this Amendment. The Examiner is asked to consider the new references and make them of record in this application.

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

PATENT
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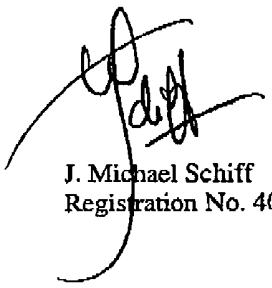
Docket 093/005p

Fees Due

Accompanying this Amendment is a fee calculation sheet, authorizing the Commissioner to charge applicant's deposit account for the Terminal Disclaimer fee.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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Enclosures: Information from the ATCC website (7 pages)
Information from Webster's Online Dictionary (1 page)